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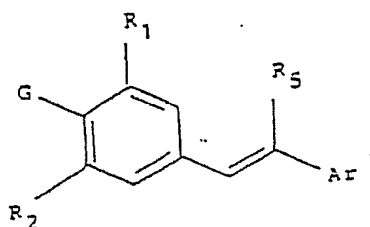
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54 Compounds for inhibiting the biosynthesis of lipoygenase-derived metabolites of arachidonic acid.

57 Compounds having the formula



inhibit 5-lipoxygenase and are useful in the treatment of inflammation.

EP 0 334 119 A1

COMPOUNDS FOR INHIBITING THE BIOSYNTHESIS OF LIPOXYGENASE-DERIVED METABOLITES OF ARACHIDONIC ACID

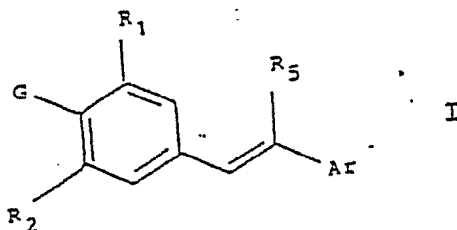
This invention relates to compounds, compositions and methods useful in treating symptoms of immunological and non-immunological disorders such as allergy, inflammation, shock or other disorders wherein metabolites of arachidonic acid are implicated.

The antigenic challenge of sensitized tissue, or damage induced in normal tissue through inflammatory insults or trauma, results in a broad array of tissue responses, including the production of various chemical mediators. One such mediator is slow reactive substance of anaphylaxis (SRS-A), the main components of which are the leukotrienes LTC₄, LTD₄ in humans and additionally LTE₄ in certain other species. Other important mediators are LTB₄ and other hydroxy and polyhydroxy metabolites of arachidonic acid which have been identified as being implicated in inflammatory processes.

The synthesis of these mediators in tissue initially requires the production of the biological precursors, arachidonic acid, as by action of phospholipase on cell membrane phospholipids. Subsequent metabolism of arachidonic acid by the lipoxygenase enzymes yields the unstable hydroperoxyeicosatetraenoic acids (HPETE's), subsequently the hydroxyeicosatetraenoic acids (HETE's), and various leukotrienes, those which make up SRS-A. Arachidonic acid is also metabolized through the alternative cyclooxygenase pathway to yield the prostaglandins and the thromboxanes.

The primary pharmacological effects of SRS-A include smooth muscle contraction and increased vascular permeability. Its implication in human allergic asthma has been recognized for many years. More recently, SRS-A, LTB₄ and the (poly)hydroxymetabolites of arachidonic acid have been associated with shock, cardiovascular disease and ischemic tissue damage.

According to a broad aspect of the present invention we provide compounds having the general formula



wherein

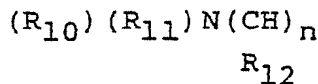
R₁ and R₂ are each independently branched or straight chained alkyl, allyl, alkoxy e.g. methoxy or halogen,

R₅ is hydrogen, alkyl or -CO₂R₈, wherein R₈ is hydrogen or C₁-C₃ alkyl

G is

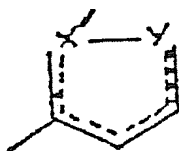
a) -OH

b) the group R₃CO₂- wherein R₃ is (i) HO₂C-X wherein X is an optionally substituted hydrocarbon chain with or without heteroatoms, or (ii) the group



wherein R₁₀ and R₁₁ are hydrogen or alkyl, R₁₂ is hydrogen, alkyl or aryl possibly containing heteroatoms or R₁₀ and R₁₂ together form a ring, or

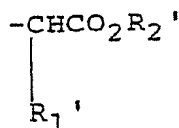
c) the group HCO₂- provided R₅ is -CO₂R₈ and R₈ is hydrogen or C₁-C₃ alkyl, and Ar is an optionally substituted heteroaromatic or aromatic ring, with proviso that Ar is not



wherein --- is single or double bond and X' and Y are

(i) \overline{N}

(ii) NR_4 , where R_4 is H, lower alkyl,



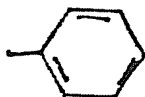
where R_1' and R_2' may be the same or different and are H or lower alkyl,

$C(O)R_4$, wherein R_4 is hydrogen and lower alkyl, cycloalkyl of from three to twenty carbons having from three to eight ring carbons, aryl or aralkyl;

(iii) O; or

(iv) S;

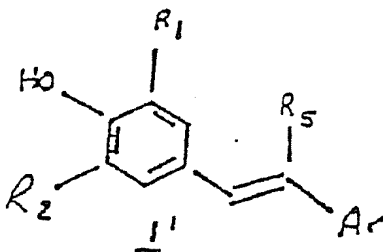
and the further proviso Ar is not



when R_1 and R_2 are both methyl,

or another pharmaceutically acceptable ester or pro-drug thereof or salt or acid addition salt of the foregoing compounds.

This invention thus relates inter alia to novel 4-(2-aryl- ethenyl)-2,6-disubstituted phenols of general formula 1:



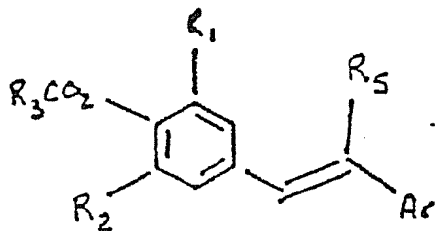
wherein R_1 and R_2 are straight or branched chained alkyl e.g. C_1 - C_3 alkyl, allyl, alkoxy or halogen, R_5 is hydrogen, alkyl, preferably C_1 - C_5 alkyl or CO_2R_8 , wherein R_8 is hydrogen or alkyl, and Ar is an optionally substituted heteroaromatic or aromatic ring.

This invention includes also the pharmaceutically acceptable esters, pro-drugs, salts and acid addition salts of the compounds of formula 1. For instance the invention also relates to esters (formulae 2a, 2b and 2c) of the compounds of formula 1, where the ester group imparts desirable physicochemical characteristics in the molecule, such as improved solubility. The esters are cleaved in vivo, releasing the compound 1 (i.e., they are pro-drugs).

In this specification unless otherwise specified the term "alkyl" means an alkyl group containing up to 8 carbon atoms e.g. up to 5 or 6 or 7 carbon atoms; and the term "lower alkyl" means an alkyl group containing 1 to 5 preferably 1 to 3 carbon atoms; "alkoxy" means an alkoxy group containing up to 8 carbon atoms preferably up to three carbon atoms and is especially methoxy; "halogen" means chlorine,

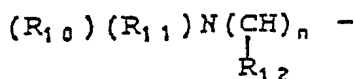
bromine or fluorine preferably chlorine, bromine or fluorine; "heteroaromatic ring" means an aromatic group containing 5 to 12 e.g. up to 9 ring members of which up to 3 may be heteroatoms chosen from N, S or O and which may contain two fused rings; "aromatic ring" means an aromatic group containing five to 12 carbon atoms e.g. up to 10 carbon atoms and which may contain two fused rings; heteroatom includes nitrogen, sulphur or oxygen atoms; the substituents on the group Ar may be for example up to three groups which may be the same or different and chosen from C₁-C₅ alkoxy e.g. C₁-C₃ alkoxy, halogen, trifluoromethyl, alkyl and arylalkoxy.

The pro-drugs of the present invention can e.g. be of three types: monoesters of dicarboxylic acids (2a), esters of amino acids (2b), and substituted olefin esters or acids (2c), and also include salts of 2a, 2b and 2c, and alkyl or other esters of the acids of 2a and 2c.



2a R₁, R₂, R₅, and Ar are as defined in Formula 1; R₃ is HO₂C-X-, where X is an optionally substituted hydrocarbon chain with or without heteroatoms,

2b R₁, R₂, R₅, and Ar are as defined in Formula 1; R₃ is



wherein R₁₀, R₁₁ are hydrogen or alkyl preferably C₁-C₃ alkyl, R₁₂ is hydrogen, alkyl preferably C₁-C₃ alkyl, or aryl, with or without heteroatoms, or R₁₁, R₁₂ form a ring, and n is an integer from 1 to 5;

2c R₁, R₂ and Ar are as defined in Formula 1; R₃ is hydrogen, or as in 2a, or as in 2b; and R₅ is CO₂R₈, wherein R₈ is hydrogen or alkyl.

Compounds of the invention are inhibitors of the enzyme 5-lipoxygenase and, accordingly, may be employed in the treatment of inflammation and in diseases where products of 5-lipoxygenase metabolism play a role, such as asthma, psoriasis, rheumatoid arthritis and inflammatory bowel disease. Compounds of formula 1 also inhibit the enzyme cyclooxygenase, although they are generally more potent in inhibiting 5-lipoxygenase.

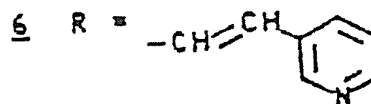
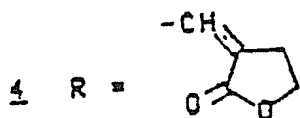
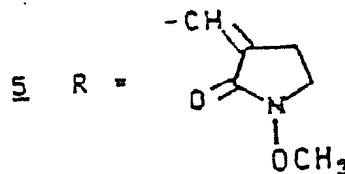
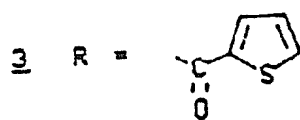
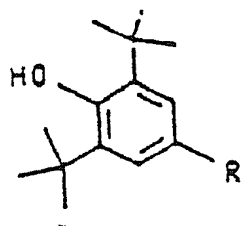
The prior art contains references for six compounds of general Formula 1 wherein Ar is a substituted phenyl ring or pyridyl ring and R₁ and R₂ are both C₁-C₃ alkyl, and one compound wherein R₁ is allyl, R₂ is methoxy and Ar is phenyl. For example, one prior art compound (R₁ and R₂ are methyl, and Ar is 4-hydroxy-3-methoxyphenyl) was disclosed as generated by the treatment of spruce wood meal with alkali (2.2M NaOH) or white liquor (2.1 M NaOH, 0.2 M Na₂S₂O₅ in the presence of 2,6-xyleneol (J. Gierer et al., Acta. Chem. Scand., Ser. B, 1979, B33 (8), 580. C.A. 92:78366t, 1980). Another prior art compound (R₁ and R₂ are methyl, and Ar is 3,5-dimethyl-4-hydroxyphenyl) is one of many symmetrical stilbene derivatives synthesized by condensation of chloroacetaldehyde with aromatic compounds, followed by re-arrangement. (R.H. Sieber, Justus Liebigs Ann. Chem. 1969, 730, 31). The oxidation of the 2,6-dialkyl-4-methylphenol with silver carbonate, followed by reduction of the resulting stilbene quinone with zinc in acetic acid is also reported as generating such prior art compound and a further prior art compound wherein R₁ and R₂ are isopropyl and Ar is 3,5-diisopropyl-4-hydroxyphenyl (V. Balogh et al. J. Org. Chem. 1971, 36, 1339).

The synthesis of prior art compounds wherein R₁ and R₂ are methyl, or R₁ is allyl and R₂ is methoxy, and Ar is phenyl by Grignard reaction of the phenolic aldehyde with benzyl magnesium bromide followed by dehydration with potassium hydrogen sulfate has been reported (H.D. Becker, J. Org. Chem. 1969, 34, 1211). The compounds are used as intermediates for dehydrogenation to bisquinone methides.

Two prior art pyridyl compounds (R₁ and R₂ are isopropyl, and Ar is 2-pyridyl or 4-pyridyl) are reportedly synthesized by condensation of the phenolic aldehyde with N-acyl picolinium salts (G.N. Bogdanov et al., Khim Geterotsikl. Soedin., 1971, 7, 1660 CA 76: 153516, 1972). Such compounds are

reported to be useful as antioxidants and useful as anti-tumor agents.

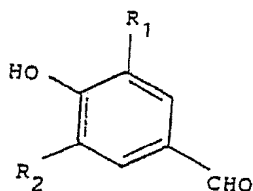
Certain derivatives of 2,6-di-t-butylphenol are reported to be dual inhibitors of the enzymes cyclooxygenase and 5-lipoxygenase. All of these are more potent inhibitors of cyclooxygenase than lipoxygenase, and accordingly useful primarily as cyclooxygenase-inhibiting, non-steroidal anti-inflammatory agents. These 2,6-di-t-butylphenol derivatives include compounds having the following formulas shown below: 3 - (G.G.I. Moore and K.F. Swingle, Agents Actions, 1982, 12, 674.); 4 (T. Hidaka et al., Jap. J. Pharmacol. 1984, 36, 77.); 5 (H. Shirota et al., Third International Conference, Inflammation Research Association Poster Session, Nos. 15 and 16, White Haven, Pa. 1986); and 6 (E. Lazer, U.S.S.N. 843,898).



The compounds of the present invention distinguish themselves from compounds having formulas 3 through 6 by being more potent and selective inhibitors of 5-lipoxygenase.

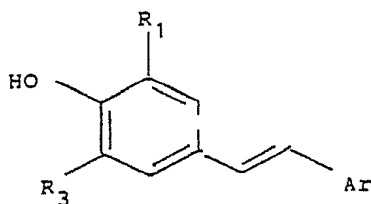
According to another aspect of the present invention there is provided a process for the preparation of compounds of the present invention which comprises

a) to prepare a compound of formula 1 wherein R₅ is hydrogen and G is -OH, reacting a compound of formula 7



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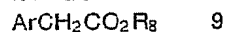
with an aryl or heteroaryl acetic acid 8
ArCH₂CO₂H 8
to yield a compound of formula 1" having the structure



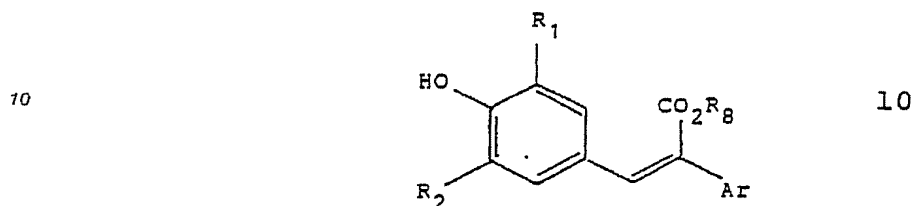
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wherein Ar, R₁ and R₂ are as defined above,

b) to prepare a compound of formula 1, wherein R₅ is CO₂R₈ and G is -OH, reacting a compound of formula 7 as defined above with an aryl or heteroaryl acetic acid ester having the formula 9



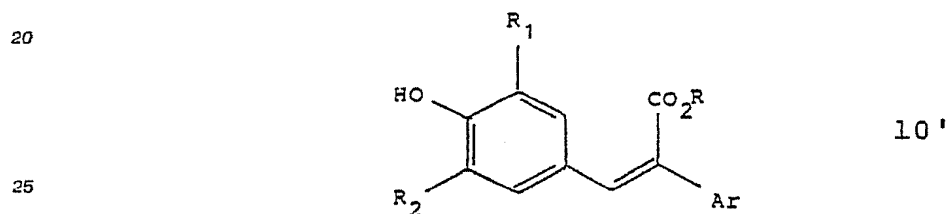
5 to yield a compound having formula 10



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wherein Ar, R₁, R₂ are as defined above and R₈ is C₁-C₃ alkyl,

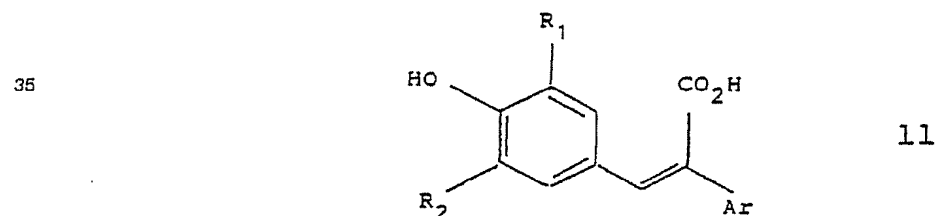
c) to provide a compound of formula 1 wherein R₈ is hydrogen, hydrolysing an ester of formula 10'



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wherein R, which may be R₈ when this is C₁-C₃ alkyl, is an ester forming group capable of being removed in a manner known per se, to yield the free acid 11

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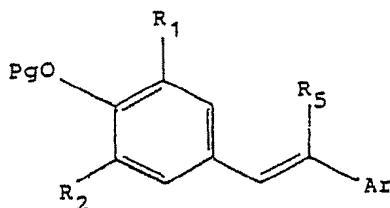
wherein Ar, R₁ and R₂ are as defined above:

d) to provide a compound of formula 1 wherein R₅ is hydrogen, decarboxylation of an acid of formula 11 to yield a compound of formula 1

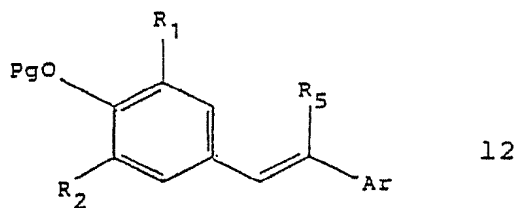
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e) to yield a compound of formula 1 wherein R₅ is C₁-C₅ alkyl, deprotecting a compound having the formula 12

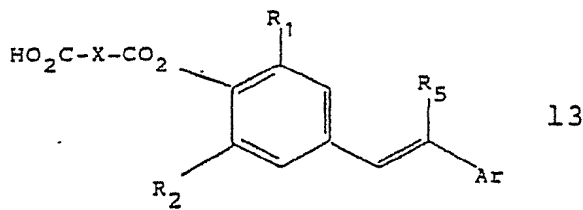
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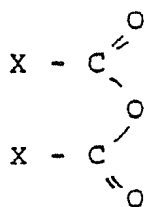
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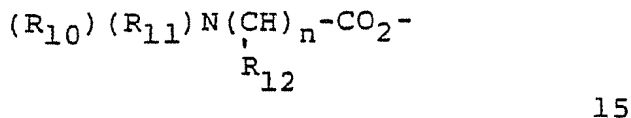
10 wherein R_1 , R_2 and Ar are as defined above and Pg is a hydroxy protecting group
f) to yield a compound of formula 13



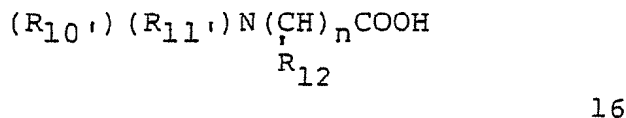
reacting a compound of the formula wherein G is OH with a compound of the formula



g) to prepare a compound of formula 1 wherein G is the group



40 as defined above,
reacting a compound of the formula 1 wherein G is OH and R_5 is alkyl, or a compound of formula 10' as
defined above with a compound of the formula



50 wherein R_1 , R_2 and R_5 are as defined above, R_{10} , and R_{11} , are hydrogen or alkyl with the proviso that if
one is hydrogen the other is alkyl or a removable protecting group, and R_{12} is hydrogen, alkyl or aryl which
may contain at least one heteroatom, and wherein R_{11} , and R_{12} may together form a ring, and n is an
integer from one to five, and thereafter removing the groups R_{10} , and/or R_{11} , when these are protecting
groups and if necessary or desired removing the group R;

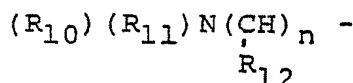
55 and thereafter, if desired, treating the product of process a) to g) by one or more of the following finishing
steps in any desired order:

i) removing an ester group R_8 to yield a free acid

ii) esterifying a free acid to yield a pharmaceutically acceptable ester wherein the ester group is capable of being cleaved *in vivo* to yield the free acid

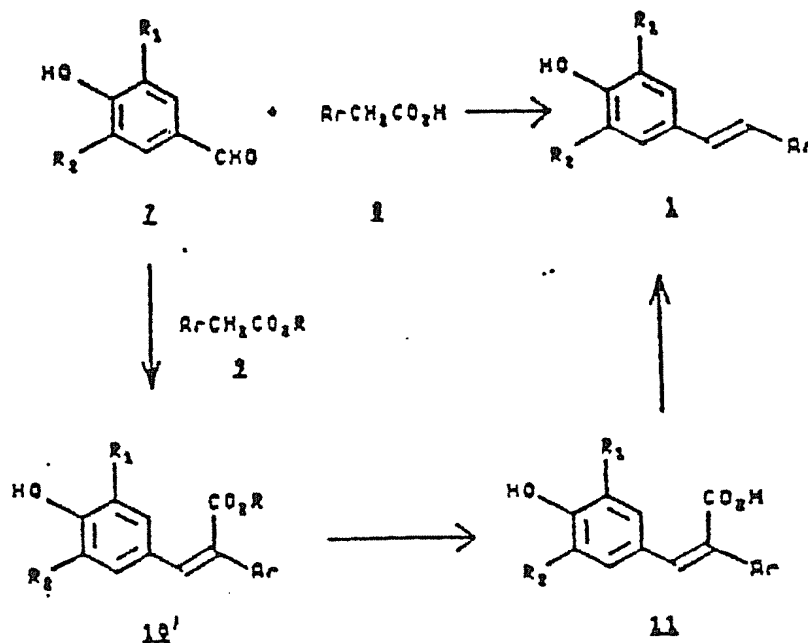
iii) forming a pharmaceutically acceptable salt of the free acid e.g. the salt of an alkali metal or alkaline earth metal e.g. sodium, potassium or calcium

iv) forming an acid addition salt of a compound of formula 1 in particular such a compound wherein R_3 is the group

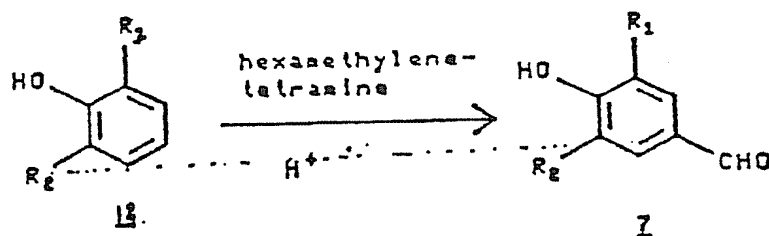


Thus the compounds of the present invention can be prepared by reaction of an appropriately substituted phenolic aldehyde 7 with an aryl- or heteroaryl acetic acid 8 in the presence of a basic catalyst, as shown below. A suitable catalyst would be for example piperidine, morpholine or triethylamine. The reaction may be performed in the presence of an inert solvent, such as methylene chloride, chloroform or benzene, which may be added at the beginning of the reaction to facilitate mixing, and then boiled off as the reaction progresses. The reaction may also be carried out in a refluxing solvent, such as toluene, xylene, or ethylenedichloride.

The compounds of the invention may also be prepared by reaction of 7 with an aryl- or heteroaryl acetic acid ester 9 in the presence of a basic catalyst and an inert solvent, as shown below. Again, a suitable catalyst would be piperidine. An inert solvent could be ethanol. The resulting ester 10 is hydrolyzed to carboxylic acid 11, which is decarboxylated to yield 1. Intermediates 10 and 11 can also be prodrugs of formula 2c, the prodrug described above.



The required substituted phenolic aldehydes (7) are prepared from the corresponding substituted phenols (12) by reaction of the phenols with hexamethylenetetramine in the presence of an acid catalyst. [Duff reaction, J.C. Duff, J. Chem Soc. 574 (1941)]. As examples, the acid used may be acetic acid, which can be used as the reaction solvent, or boric acid in ethylene glycol as solvent followed by hydrolysis. These modified conditions for the Duff reaction are reported in the literature. The required phenols (12) and arylacetic acids (7) are available commercially or may be prepared by methods reported in the literature.



10 For the compounds of formula 1 where R_2 is methyl or n-butyl, the compounds may be prepared via a Wittig reaction; i.e., a protected phenolic aldehyde (e.g., an ethyl carbonate derivative) is reacted with a Wittig salt of the corresponding phenyl derivative with a base catalyst, such as n-butyllithium, in a suitable solvent such as ether, followed by deprotection e.g. by hydrolysis of the carbonate, to yield the phenol. The remaining compounds of formula 1 may be prepared using materials and techniques well within the ability of one skilled in the art.

15 The prodrug esters of formula 2a may be prepared by standard procedures, for example by reaction of a phenol of formula 1 with an anhydride in the presence of a base in an inert solvent. The prodrug esters of formula 2b may be prepared by standard procedures, for example by reaction of a phenol of formula 1 with a protected amino acid in the presence of a coupling reagent such as dicyclohexylcarbodiimide in an inert solvent. A basic catalyst such as 4-dimethylaminopyridine may be added. The protecting group is then removed from the amino acid by standard procedures. The protecting group used may be one of those generally employed in peptide chemistry. For example, tert-butyloxycarbonyl, benzyloxycarbonyl, 9-fluorenylmethyloxycarbonyl or biphenylisopropylloxycarbonyl may be used as amino-protecting groups. See The Practice of Peptide Synthesis, M. Bodanszky and A. Bodanszky (Springer-Verlag, 1984). The prodrugs of formula 2c may be formed by reaction of an aldehyde of formula 7 with an arylacetic ester, formula 9, in a refluxing solvent in the presence of a basic catalyst. A suitable refluxing solvent is ethanol, for example. A suitable basic catalyst is piperidine, for example.

20 The compounds according to the present invention may be administered to warm-blooded animals topically, perorally, parenterally, rectally or by the respiratory route as active ingredients in conventional pharmaceutical compositions, that is, compositions comprising a pharmaceutical carrier or excipient and an effective amount of the active ingredient.

25 In another aspect, the present invention provides pharmaceutical compositions comprising a compound of formula 1 or a physiologically acceptable salt thereof, together with at least one pharmaceutical carrier or excipient.

30 In a still further aspect, the invention provides a method of treatment of humans or other warm-blooded animals to combat allergic or inflammatory reactions therein which method comprises administering thereto an effective amount of a compound of formula 1 or a physiologically acceptable salt thereof.

35 In a yet still further aspect the invention provides the use of a compound of formula 1 or a physiologically acceptable salt thereof for the treatment of allergic or inflammatory reactions of humans or other warm-blooded animals.

40 When the compounds of the invention are given by the oral route, they may be formulated in the form of syrups, tablets, capsules, pills and the like. Preferably, the compositions are in unit dosage form, or in a form in which the patient can administer to himself a single dose. When the composition is in the form of a tablet, powder or lozenge, any pharmaceutical carrier suitable for formulating solid compositions may be used. Examples of such carriers are various starches, lactose, glucose, sucrose, cellulose, dicalcium phosphate, and chalk. The composition may also be in the form of an ingestible capsule (for example of gelatin) containing the compound; or in the form of a syrup, a liquid solution or a suspension. Suitable liquid pharmaceutical carriers include ethyl alcohol, glycerin, saline, water, propylene glycol or sorbitol solution, which may be compounded with flavoring or coloring agents to form syrups.

45 The compounds of this invention may also be administered by other than the oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example, for rectal administration as a suppository or for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, such as sterile, pyrogen-free water of a parenterally acceptable oil or a mixture of liquids, which may contain bacteriostatic agents, antioxidants, preservatives, buffers, or other solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose forms such as ampules or disposable injection devices or in multi-dose vials such as a bottle from which the appropriate dose may be withdrawn, or in solid form or concentrate which can be used to prepare

an injectable formulation.

Compounds of this invention may also be suitably presented for administration to the respiratory tract as an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compounds suitably have diameters of less than 20 microns, preferably less than 10 microns. Where appropriate, small amounts of other anti-allergics, anti-asthmatics and bronchodilators, for example, sympathomimetic amines such as isoprenaline, isoetharine, metaproterenol, salbutamol, phenylephrine, fenoterol and ephedrine; xanthine derivatives such as theophylline and aminophylline; corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

Compounds of this invention may also be presented as an ointment, cream, lotion, gel, aerosol or solution for topical application to the skin, nose, or eye.

For the preparation of pharmaceutical compositions, the compounds of the invention are mixed in the usual way with appropriate pharmaceutical carrier substances and aroma, flavoring and coloring materials and formed, for example, into tablets or capsules or, with the addition of appropriate adjuvants, suspended or dissolved in water or in an oil, for example corn oil.

The compounds of this invention can be administered orally and parenterally in liquid or solid form. As injection medium, it is preferred to use water which contains the stabilizing agents, solubilizing agents and/or buffers conventionally used for injection solutions. Additives of this type include, for example, tartrate, citrate and acetate buffers, ethanol, propylene glycol, polyethylene glycol, complex formers (such as EDTA), antioxidants (such as sodium bisulfate, sodium metabisulfate or ascorbic acid), high-molecular-weight polymers (such as liquid-polyethylene oxides) for viscosity regulation, and polyethylene derivatives of sorbitol anhydrides.

Preservatives may also be added, if necessary, such as benzoic acid, methylene propylparaben, benzalkonium chloride or other quaternary ammonium compounds.

Solid carrier materials which can be used include, for example, starch, lactose, mannitol, methyl cellulose, microcrystalline cellulose, talcum, pyrogenic silica, dicalcium phosphate, and high-molecular-weight polymers (such as polyethylene glycol).

The following examples demonstrate reaction conditions under which compounds of the present invention may be prepared. Such examples are illustrative only, and do not limit the scope of the present invention.

Example 1

3,5-Dimethyl-4-hydroxybenzaldehyde

2,6-Dimethylphenol (50g, 0.41 mol) and hexamethylenetetramine (57g, 0.41 mol) were combined in 400 mL acetic acid and heated to reflux for 4.5 hours. The reaction mixture was poured into 1500 mL water and stirred until a precipitate formed. The mixture was refrigerated overnight, filtered, and the solid product dried and recrystallized from EtOH. Two crops of 3,5-Dimethyl-4-hydroxybenzaldehyde were obtained for a total of 19.02g (0.127 mol, 31%), mp 114-115 °C

Example 2

The compound in Example 1 may also be prepared under the following conditions: 2,6-Dimethylphenol (100g, 0.818 mol), hexamethylenetetramine (195g, 1.39 mol) and boric acid (270g, 4.37 mol) were combined in 1,000 mL ethylene glycol and heated at 130 °C, with stirring, for 1 hr. The hot reaction mixture was combined with 1,400 mL 30% H₂SO₄ and stirred overnight at ambient temperature. The precipitated product was filtered, rinsed with water and recrystallized from EtOH giving 85g, 3,5-dimethyl-4-hydroxybenzaldehyde (0.54 mol, 66%), mp 112-113 °C

Example 3

3-Ethyl-5-methoxy-4-hydroxybenzaldehyde

2-Ethyl-6-methoxyphenol (11.4g, 0.075 mol) and hexamethylenetetramine (10.5g, 0.075 mol) were combined in 65 mL acetic acid and heated to reflux for 4.5. hours. The reaction mixture was poured onto ice and water, and the product extracted into CH₂Cl₂ (3 x 150 mL). The combined organic extracts were washed with saturated NaCl solution, dried (Na₂SO₄) and concentrated in vacuo. The product was recrystallized from EtOH giving 2.53g. Crude product from the mother liquor was purified by column chromatography on silica gel, eluting with CH₂Cl₂, giving another 2.1 g for a total of 4.63 g, (0.026 mol, 34%).

The following examples are illustrative of the general procedures used to prepare the compounds of this invention (General Formula 1) which are listed in Table 1.

Example 4

2,6-Dimethyl-4-[2-(2-thienyl)ethenyl]phenol

Piperidine (58g, 0.68 mol) was added to 2-thiopheneacetic acid (34g, 0.24 mol) suspended in 75 mL CH₂Cl₂. 3,5-Dimethyl-4-hydroxybenzaldehyde (30g, 0.2 mol) was added and the mixture was heated in an oil bath (bath temperature: 130 °C) with mechanical stirring, under N₂. The CH₂Cl₂ was allowed to boil off. After heating for 7 hours, the dark brown residue was eluted through a silica gel column with CH₂Cl₂. The major fraction was concentrated, and the product recrystallized from toluene giving 21.5g 2,6-Dimethyl-4-[2-(2-thienyl)ethenyl]phenol, (0.093 mol, 47%) mp 133-134 °C.

Anal: Calcd. for C ₁₄ H ₁₄ OS:						
	C	73.01;	H	6.13;	S	13.92
Found:	C	73.04;	H	6.02;	S	13.98

¹H NMR: 2.3 (6H, s, CH₃), 4.7 (1H, s, OH), 6.75-7.2 (7H, aromatic and olefinic protons).

Example 5

The product of Example 4 may also be prepared by the following procedure:

2-Thiopheneacetic acid (15g, 0.105 mol) and piperidine (12.9g, 0.15 mol) were combined in 450 mL to and stirred for 20 minutes. 3,5-Dimethyl-4-hydroxybenzaldehyde (15g 0.100 mol) was added and the reaction mixture heated to reflux with a Dean-Stark trap attached to remove water formed in the reaction. After 20 hours, the mixture was cooled to room temperature and poured onto a pad of silica gel packed 3/4 full onto a 2L fritted glass filtering funnel. The product was eluted with toluene and the light yellow solid was recrystallized from ligroine giving 14g 2,6-dimethyl-4-[2-(2-thienyl)ethenyl]phenol, (0.061 mol, 61%), mp 133-134 °C.

Anal: Calcd. for C ₁₄ H ₁₄ OS:						
	C	73.01;	H	6.13;	S	13.92
Found:	C	73.19;	H	6.18;	S	13.97

¹H NMR: 2.3 (6H, s, CH₃), 4.7 (1H, s, OH), 6.75-7.2 (7H, aromatic and olefinic protons).

Example 5a

Ethyl 3-(3,5-dimethyl-4-hydroxyphenyl)-2-(2-thienyl)propenoate

A mixture of 3,5-dimethyl-4-hydroxybenzaldehyde (15g, 0.1 mol), ethyl 2-thiopheneacetate (17.9 g, 0.105 mol), piperidine (9g, 0.105 mol) and p-toluenesulfonic acid (100 mg) in 300 mL EtOH was heated to

reflux for 18 hours. The reaction mixture was concentrated down to about half its original volume on a rotary evaporator, and a precipitate formed. The mixture was stored in the freezer overnight, filtered and the solid rinsed with cold EtOH. The solid was then suspended in water, the mixture made acidic with 1N HCl and the solid filtered and dried giving 12.2g ethyl 3-(3,5-dimethyl-4-hydroxyphenyl)-2-(2-thienyl) propenoate, (0.04 mol, 40%) mp 85-87° C. A small sample was recrystallized from EtOH, mp 87-89° C.

Anal: Calcd. for C ₁₇ H ₁₈ O ₃ S:						
	C	67.52	H	6.00	S	10.60
Found:	C	67.64	H	6.00	S	10.62

¹H NMR; 1.3 (3H, t, CH₃), 2.05 (6H, s, CH₃), 4.26 (2H, q, CH₂), 5.0 (1H, s, OH), 6.8-7.8 (6H, aromatic and olefinic protons).

Example 5b

3-(3,5-Dimethyl-4-hydroxyphenyl)-2-(2-thienyl)propenoic acid

A mixture of ethyl 3-(3,5-dimethyl-4-hydroxyphenyl)-2-(2-thienyl)-propenoate (1.5g, 5 mmol) 10 mL 2N NaOH and 10 mL EtOH was heated to reflux for 3.5 hours. The reaction mixture was then concentrated to half its original volume and combined with 15 mL 2N HCl while stirring on an ice bath. The resulting solid was filtered, dried and recrystallized from toluene giving 0.97g 3-(3,5-dimethyl-4-hydroxyphenyl)-2-(2-thienyl) propenoic acid (3.5 mmol, 71%), mp 195-197° C.

Anal: Calcd. for C ₁₅ H ₁₄ O ₃ S:						
	C	65.67	H	5.14	S	11.69
Found:	C	65.60	H	5.08	S	11.60

¹H NMR: 2.0 (6H, s, CH₃), 6.7-7.7 (6H, aromatic and olefinic protons), 8.8 (1H, s, OH), 12.6 (1H, s, CO₂H).

Example 5c

The product of Example 4 may also be prepared by the following procedure:
3-(3,5-dimethyl-4-hydroxyphenyl)-2-(2-thienyl)propenoic acid (5.3g, 19.3 mmol) was combined with piperidine (1.7g, 20 mmol), forming a light brown mass. Toluene (200 mL) was added and the reaction stirred at room temperature for 20 minutes and then refluxed for 40 hours. The reaction mixture was concentrated to half its original volume and passed through a glass funnel containing silica gel (250g) and eluted with toluene. The light yellow fractions containing product were concentrated giving 1.98g 2,6-dimethyl-4-[2-(2-thienyl)ethenyl]phenol (1a, Table 1), (8.6 mmol, 44% mp 132-133° C). The ¹H NMR spectrum was identical to the one in Example 4.

Example 6

2-Methoxy-6-methyl-4-[2-(2-thienyl)ethenyl]phenol

Piperidine (2.7g, 32 mmol) was added to a suspension of 2-thiopheneacetic acid (3.3g, 23 mmol) in 10 mL CH₂Cl₂, followed by 3.5g (21 mmol) 4-hydroxy-3-methoxy-5-methylbenzaldehyde. The stirred mixture was heated on an oil bath, the temperature of the oil bath was allowed to rise to 135° C over 3-4 hr. After 2 hours additional piperidine (2.6g, 30 mmol) was added. The reaction mixture was removed from the oil bath after about 4.5 hours. The residue was taken up in 100 mL EtOAc, and washed with 1N HCL (100 mL), water (100 mL), saturated NaHCO₃ (100 mL), 1N HCl (75 mL), saturated NaCl solution (100 mL), dried

(Na₂SO₄) and concentrated. The residue was recrystallized twice from EtOH giving 0.95g 2-methoxy-6-methyl-4-[2-(2-thienyl)ethenyl]phenol (3.9 mmol, 18%), mp 113-114 °C.

Anal: Calcd. for C ₁₄ H ₁₄ O ₂ S:						
	C	68.26	H	5.74	S	13.02
Found:	C	68.63	H	5.78	S	12.89

¹H NMR: 2.25 (3H, s, CH₃), 3.9 (3H, s, CH₃), 5.7 (1H, s, OH), 6.8-7.2 (7H, aromatic and olefinic protons).

Example 7

2,6-Diethyl-4-[2-(2-thienyl)ethenyl]phenol

A mixture of 3,5-diethyl-4-hydroxybenzaldehyde (2.5g, 14 mmol), 2-thiopheneacetic acid (2.58g, 18.2 mmol) and piperidine (4.3g, 51 mmol) in 20 mL CH₂Cl₂ was heated in an oil bath (130-140 °C) for 2.5 hours. The reaction mixture was taken up in EtOAc (100 mL), washed with water (100 mL), the saturated NaHCO₃ solution (2 x 50 mL), saturated NaCl (50 mL), dried (Na₂SO₄) and then concentrated. The residue was passed through a silica gel column, eluting with CH₂Cl₂, the fractions containing product concentrated and the residue recrystallized from EtOH giving 1.57g 2,6-Diethyl-4-[2-(2-thienyl)ethenyl]phenol (6.1 mmol, 43%), mp 113-115 °C.

Anal: Calcd. for C ₁₆ H ₁₈ OS:						
	C	74.38	H	7.02	S	12.41
Found	C	74.24	H	7.03	S	12.36

¹H NMR: 1.25 (6H t, CH₃), 2.6 (4H, q, CH₂), 4.75 (1H, s, OH), 6.8-7.2 (7H, aromatic and olefinic protons).

The following two examples illustrate procedures by which a prodrug of type 2a or 2b may be prepared.

Example 8

2,6-Dimethyl-4-[2-(2-thienyl)ethenyl]phenyl succinate

1.47g 4-Dimethylaminopyridine (12 mmol), 1g succinic anhydride (10 mmol), and 1g triethylamine (10 mmol) were added to a solution of 1a (Table 1) (2.3g, 10 mmol) in 25 mL CH₂Cl₂. After stirring at room temperature for 2.5 hours the reaction was heated to reflux for 1 hour. Then additional 4-dimethylaminopyridine (0.5g), succinic anhydride (0.3g) and triethylamine (1g) were added and the reaction stirred at room temperature another 30 minutes. The reaction was diluted with 50 mL CH₂Cl₂, washed with 1N HCl (2 x 50 mL), saturated NaCl (50 mL), dried (Na₂SO₄) and concentrated. The residue was recrystallized from isopropanol giving 2.25g 2,6-Dimethyl-4-[2-(2-thienyl)ethenyl]phenyl succinate (6.8 mmol, 68%) mp 168-170 °C

Anal: Calcd. for C ₁₈ H ₁₈ O ₄ S:						
	C	65.43	H	5.50	S	9.70
Found:	C	65.28	H	5.48	S	9.60

¹H NMR: 2.2(6H, s, CH₃), 2.9 (4H, m, CH₂CH₂), 6.75-7.3 (7H, aromatic and olefinic protons), 11 (1H, broad s, CO₂H).

Example 9

2,6-Dimethyl-4-[2-(2-thienyl)ethenyl]phenyl glycinate hydrochloride

A mixture of 1a (Table 1) (4.6g, 20 mmol), N-(tert-butoxycarbonyl)glycine (3.5g, 20 mmol), 4-dimethylaminopyridine (0.8g, 6.5 mmol) and dicyclohexylcarbodiimide (4.2g, 20 mmol) in 175 mL CH₂Cl₂ was stirred for 16 hours at room temperature. The white precipitate was filtered off and rinsed with CH₂Cl₂. The filtrate was washed with 1N HCl (2 x 75 mL), saturated NaHCO₃ solution (1 x 75 mL) and saturated NaCl solution (1 x 75mL) dried (Na₂SO₄) and concentrated. The residue was recrystallized from ethanol giving 5.6g of the protected glycine ester (14.5 mmol, 72% mp 124-125° C).

3.8g of the protected glycine ester (9.8 mmol) was dissolved in 250 mL anhydrous ether and HCl gas was bubbled in, with stirring for 30 minutes. The reaction was stirred for 18 hours at room temperature, then the precipitated product was filtered. After stirring the filtrate another 24 hours, additional product was collected for a total of 3.1g 2,6-dimethyl-4-[2-(2-thienyl)ethenyl]phenyl glycinate hydrochloride (9.6 mmol, 98%) mp 275-277° C.

Anal: Calcd. for C₁₆H₁₇NO₂S•HCl:

	C	59.34	H	5.60	Cl	10.95	N	4.33	S	9.90
Found:	C	58.97	H	5.64	Cl	11.38	N	4.38	S	9.72

¹H NMR: 2.1 (6H, s, CH₃), 4.25 (2H, s, CH₂), 6.8-7.5 (7H, aromatic and olefinic protons), 8.6 (3H, s, NH₃⁺).

Inhibition of 5-Lipoxygenase in Human Polymorphonuclear Leukocytes (PMN's)

The inhibition of 5-lipoxygenase is measured by determining whether and to what extent test compounds inhibit the amount of 5-HETE biosynthesized by human PMN's. 5-HETE biosynthesis serves as a marker for arachidonic acid metabolism by 5-lipoxygenase.

Human PMN's (5 x 10⁶ cells/0.5 mL) in pH 7.2 phosphate buffer containing Ca²⁺ (0.6 mM) and Mg²⁺ (1.0 mM) were incubated with test compound for 15 minutes at 37° C with shaking. Calcium ionophore A23187 (0.25 mM, 0.01 mL) and [¹⁴C] arachidonic acid (0.10 microCi in 0.025 mL 0.01N NaOH) were added, and the mixture incubated another 2.5 minutes. The reaction was terminated by the addition of 0.025 mL of 1.0 N HCl. The mixture was then extracted with ethyl acetate-methylene chloride (2:3) supplemented with 12 microgram/mL cold arachidonic acid to reduce degradation of the metabolites. After concentrating the organic phase, the number of microlitres containing 5 x 10⁴ cpm was determined and that volume applied to a silica gel plate. The plate was developed in methylene-chloride-methanol-acetic acid-water (90:8:1:0.8), air dried, and counted on a Berthold linear TLC analyzer. The integrated area of the 5-HETE band was determined and compared with the control (no drug).

Table 1 shows the percent inhibition of 5-lipoxygenase by compounds of the invention at test concentrations of 1 microM. In cases where the IC₅₀ was determined, the result is shown in microM.

Table 1: Inhibition of 5-lipoxygenase by Compounds of General Formula 1

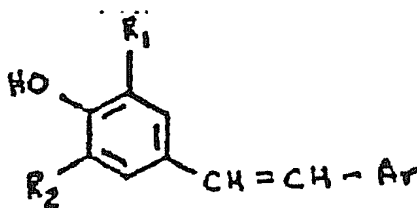


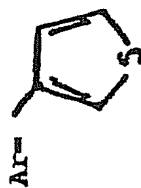
TABLE I

Compound No. R₁ R₂ X Formula mp(C°) Inhibition of 5-LO
% at 1 M IC₅₀ (M)

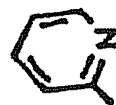


1a	CH ₃	CH ₃	H	C ₁₄ H ₁₄ OS	133-134	91	0.07
1b	CH ₃	CH ₃	Cl	C ₁₄ H ₁₃ ClOS	125-126	77	
1c	CH ₃	CH ₃	CH ₃	C ₁₅ H ₁₆ OS	104-105	62	
1d	CH ₃	OCH ₃	H	C ₁₄ H ₁₄ O ₂ S	113-114	65	0.08
1e	CH ₃ CH ₂	OCH ₃	H	C ₁₅ H ₁₆ O ₂ S	85.5-86.5	85	0.11
1f	CH ₃ CH ₂ CH ₂	OCH ₃	H	C ₁₆ H ₁₈ O ₂ S	99-100	76	0.14
1g	CH ₃	OCH ₃	Cl	C ₁₄ H ₁₃ ClO ₂ S	90-91	76	
1h	CH ₂ =CH-CH ₂	CH ₃	H	C ₁₆ H ₁₆ OS	79-80	70	0.1
1i	CH ₃ CH ₂	CH ₃ CH ₂	H	C ₁₆ H ₁₈ OS	113-115	70	
1j	(CH ₃) ₂ CH	(CH ₃) ₂ CH	H	C ₁₈ H ₂₂ OS	45.5-48.5	78	0.6
1k	CH ₃	F	H	C ₁₃ H ₁₁ FOS	86-88	65	
1l	CH ₃	Cl	H	C ₁₃ H ₁₁ ClOS	109.5-110.5	84	
1m	OCH ₃	F	H	C ₁₃ H ₁₁ FO ₂ S	82-83	65	
1n	OCH ₃	OCH ₃	H	C ₁₄ H ₁₄ O ₃ S	95-96.5	78	

Compound R₁ R₂ Formula mp(C°) Inhibition of 5-LO
No. % at 1 M IC₅₀ (M)



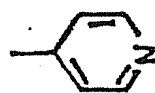
lo	CH ₃	CH ₃	C ₁₄ H ₁₄ OS	144-145	84	0.07
lp	CH ₃	OCH ₃	C ₁₄ H ₁₄ O ₂ S	128-130	70	
lq	OCH ₃	OCH ₃	C ₁₄ H ₁₄ O ₃ S	97-98	77	
lr	CH ₃ CH ₂	OCH ₃	C ₁₅ H ₁₆ O ₂ S	122-123.5	82	
ls	CH ₃	Cl	C ₁₃ H ₁₁ ClOS	104-105	75	
lt	OCH ₃	F	C ₁₃ H ₁₁ FO ₂ S	101-103	59	
lu	CH ₃ CH ₂	CH ₃ CH ₂	C ₁₆ H ₁₈ OS	130-132	66	
lv	CH ₂ =CHCH ₂	CH ₃	C ₁₆ H ₁₆ OS	97-99	75	



(p=2),




(p=3), or



(p=4):

lw	CH ₃	CH ₃	C ₁₅ H ₁₅ NO	163-164	77		p=2
lx	CH ₃	CH ₃	C ₁₅ H ₁₅ NO	144-145	62	0.5	p=3
ly	CH ₃	CH ₃	C ₁₅ H ₁₅ NO	208-209	46		p=4
lz	CH ₃	OCH ₃	C ₁₅ H ₁₅ NO ₂	144-145	52	0.9	p=3
laa	CH ₃ CH ₂	CH ₃ CH ₂	C ₁₇ H ₁₉ NO	130-131	59		p=3
lab	(CH ₃) ₂ CH	(CH ₃) ₂ CH	C ₁₉ H ₂₃ NO	136-138	73	0.6	p=3
lac	CH ₂ =CHCH ₂	CH ₃	C ₁₇ H ₁₇ NO	111-113	61		p=3

Compound No.	R ₁	R ₂	X	Formula	mp(C°)	Inhibition of 5-LO % at 1 M IC ₅₀ (M)
Ar=						
lad	CH ₃	CH ₃	H	C ₁₆ H ₁₆ O	139-141	72 0.18
lae	"	"	4-CH ₃	C ₁₇ H ₁₈ O	115-117	75 0.25
laf	"	"	4-CH ₂ CH ₃	C ₁₈ H ₂₀ O	108-109	62
lag	"	"	4-OCH ₃	C ₁₇ H ₁₈ O ₂	139-141	88 0.2
lah	"	"	4-Cl	C ₁₆ H ₁₅ ClO	146-148	76 0.3
lai	"	"	3,4-diCl	C ₁₆ H ₁₄ Cl ₂ O	145.5-147	58
laj	"	"	4-F	C ₁₆ H ₁₅ FO	141.5-143	77 0.15
lak	"	"	3-CF ₃	C ₁₇ H ₁₅ F ₃ O	109-110.5	84 1.0
lal	"	"	3-CH ₃	C ₁₇ H ₁₈ O	115-117	84 0.2
lam	"	OCH ₃	4-F	C ₁₆ H ₁₅ FO ₂	126.5-128	71
lan	"	"	3-CF ₃	C ₁₇ H ₁₅ F ₃ O ₂	72-73	44
lao	CH ₃ CH ₂	"	4-OCH ₃	C ₁₈ H ₂₀ O ₃	113-114	66
lap	"	"	4-F	C ₁₇ H ₁₇ FO ₂	121-122	49
laq	CH ₃	CH ₃	4-OBu	C ₂₀ H ₂₄ O ₂	138-139	53
lar	"	"	4-OPr	C ₁₉ H ₂₂ O ₂	127-128	81
las	"	"	X*	C ₁₉ H ₂₂ O ₃	143-145	70
lat	CH ₃ CH ₂	CH ₃ CH ₂	4-OCH ₃	C ₁₉ H ₂₂ O ₂	122.5-123.5	55
lau	"	"	4-CH ₃	C ₁₉ H ₂₂ O	113-114	70

cont.

Compound No. R_1 R_2 X Formula mp(C°) Inhibition of 5-LO
 ‡ at 1 M IC₅₀ (M)

lav	(CH ₃) ₂ CH	(CH ₃) ₂ CH	4-OCH ₃	C ₂₁ H ₂₆ O ₂	83-85	71
law	"	"	3,4-diOCH ₃	C ₂₂ H ₂₈ O ₃	161-163	57
lax	"	"	4-F	C ₂₀ H ₂₃ FO	51-53	32
lay	"	"	3-CF ₃	C ₂₁ H ₂₃ F ₃ O	55-57.5	34
laz	OCH ₃	F	4-OCH ₃	C ₁₆ H ₁₅ FO ₃	151-152	63

x* = 4-O(CH₂)₂OCH₃

Inhibition of Antigen-Induced, SRS-A Mediated Bronchoconstriction in Conscious Guinea Pigs

This model is used to measure the ability of a drug to inhibit 5-lipoxygenase *in vivo*. SRS-A (slow reacting substance of anaphylaxis - also referred to as leukotrienes C₄, D₄ and E₄) is released by cells in the sensitized guinea pig upon stimulation by antigen, resulting in bronchioconstriction and change in pulmonary function. The leukotrienes are biosynthesized from arachidonic acid by the enzyme 5-lipoxygenase. Therefore, an inhibitor of 5-lipoxygenase could reduce the production of SRS-A and attenuate the bronchioconstriction.

Male outbred Hartley strain albino guinea pigs (250-300 grams) were sensitized by i.p. injection of ovalbumin (3mg/kg) followed by an i.p. injection of Bordetella pertussis (about 5x10⁹ killed organisms) and studied 14 days later.

Sensitized guinea pigs (fasted for 18 hours) were anesthetized and a catheter-tip pressure transducer was inserted into the pleural space of each animal. The animals are pretreated (i.p.) with pyrilamine (10mg/kg) and indomethacin (10mg/kg) to antagonize the effects of histamine and inhibit cyclooxygenase respectively. Cyclooxygenase products and histamine are released endogenously along with SRS-A, upon antigen challenge. Test compound is also administered i.p., 60 minutes before antigen challenge.

The guinea pigs were placed in a "head out" plethysmograph and allowed to recover from anesthesia. Airflow into the respiratory system, pleural pressure and airflow signals were measured, and tidal volume, dynamic pulmonary compliance (C_{dyn}) and breathing frequency were calculated according to a published technique (E.G. Damen et al., Toxicol. Appl. Pharmacol., 1982, 64, 465). After baseline values for pulmonary function were obtained, the animals were challenged by aerosolized ovalbumin. The overall changes in pulmonary function parameters were determined by calculating the mean changes from baseline during the period 5 to 15 minutes following antigen challenge.

Drug efficacy was determined by comparing the mean of the percent decrease in C_{dyn} from baseline in drug treated animals (N = 4-6) to control animals (N = 10-12).

Table 2 shows the effect of several of the compounds from Table 1 in the antigen-induced, SRS-A mediated bronchioconstriction model.

TABLE 2

Compound No. ^{1,2}	% Inhibition of Bronchioconstriction ³
1a	75
1d	41
1e	51
1f	57
1o	26
1x	39
1ab	34
1ad	53
1ae	59
1ag	28
1aj	43
1al	49

1. Compound number refers to the compound numbers found in Table 1.

2. Compounds were administered i.p. in a 5% Tween 80 suspension, at a dose of 30mg/kg.

3. % inhibition of the decrease in C_{dyn} seen in antigen challenged animals.

Inhibition of Antigen-Induced, Late Phase Inflammatory Cell Infiltration in Guinea Pigs

This model is used to measure the ability of a drug to inhibit 5-lipoxygenase *in vivo*. In addition to SRS-A, a chemotactic substance LTB₄ is also released by cells in the sensitized guinea pig lung upon stimulation by antigen. As a result there is a measurable influx of cells into the lung. Therefore, an inhibitor

of 5-lipoxygenase could reduce the formation of LTB₄ and thereby reduce the cell influx into the lung.

Male outbred Hartley strain albino guinea pigs (250-300 grams) were sensitized to ovalbumin as in the procedure for inhibition of antigen-induced, SRS-A mediated bronchioconstriction in conscious guinea pigs.

Sensitized guinea pigs were fasted and pretreated with pyrilamine and indomethacin as in bronchioconstriction testing procedure. Test compounds, suspended in 1% acacia, were administered 60 minutes before antigen challenge. Four hours after challenge with aerosolized ovalbumin, the animals were anesthetized, and exsanguinated by severing of the abdominal artery and inferior vena cava. Whole lung lavage was performed with three 5 mL aliquots of normal saline buffered with sodium bicarbonate.

Total cell counts were performed on a Coulter Counter, and differential cell counts were performed. Compounds were evaluated for their ability to alter the antigen-induced total cell influx and, more specifically, neutrophil (PMN) influx.

Table 3. Inhibition of Antigen-Induced, Late Phase Inflammatory Cell Infiltration in Guinea Pigs.

TABLE 3

Compound No. ¹	Dose (mg/kg)	Route	% Inh. Total Cells	% Inh. PMN
1a	30	ip	78	95
1a	30	po	51	14
1f	30	ip	77	54
1h	10	ip	55	46
1i	30	ip	51	74
1i	30	po	65	51
2a	10	po	89	93

1. Compound No. refers to the compound numbers found in Table 1 except for 2a which refers to a prodrug wherein R₁ and R₂ are CH₃; Ar is 2-thienyl; and X is -CH₂CH₂.

Ex Vivo Inhibition of A23187-Induced LTB₄ Generation in Squirrel Monkeys.

Incubation of squirrel monkey whole blood with calcium ionophore A23187 stimulates the production of LTB₄. This LTB₄ production can be inhibited by a lipoxygenase inhibitor *in vitro* by incubating the blood with the inhibitor prior to A23187 challenge. By dosing squirrel monkeys with a lipoxygenase inhibitor prior to withdrawal of a blood sample, one can determine the ability of the lipoxygenase inhibitor to be absorbed into the bloodstream by measuring the inhibition of A23187 induced LTB₄ production *ex vivo*.

Squirrel monkeys (400-650g) were fasted for 18 hours, anesthetized and dosed either orally or intraperitoneally with test compound. After the desired time period, blood was withdrawn from the femoral vein. The blood (0.5 mL) was heparinized, preincubated at 37° C for 5 minutes and stimulated with A23187

in DMSO to give a final concentration of 30 microM. The reaction was terminated with EGTA (final concentration 10 microM), and the blood centrifuged. Levels of LTB₄ in the plasma were then determined by radioimmunoassay.

The results shown in Table 4 illustrate the ability of a prodrug of type 2a or 2b to be absorbed after ip or po dosing compared to the parent compound 1a.

TABLE 4

Table 4. Ex Vivo Inhibition of A23187-Induced LTB ₄ Generation in Squirrel Monkey Blood.						
Compound No. ¹	Dose (mg/kg)	Route	Time After Dosing(min.)	Percent Inh.		
				Monkey #1	2	3
1a	30	ip ²	60	47	12	4
1a	30	po ²	60	18	0	0
2a	30	ip ³	60	62	83	89
2a	30	po ³	60	50	71	66
2a	30	po ³	120	41	100	61
2a	30	po ³	240	43	65	100
2b	30	ip ⁴	60	78	56	69
2b	30	po ⁴	60	62	54	33 ⁵

1. Compound No. 1a refers to Compound 1a in Table 1. 2a refers to a prodrug wherein R₁ and R₂ are CH₃, Ar is 2-thienyl and X is CH₂CH₂- 2b refers to a prodrug wherein R₁ and R₂ are CH₃, Ar is 2-thienyl, R₅, R₆ and R₇ are H and n = 1, hydrochloride salt.

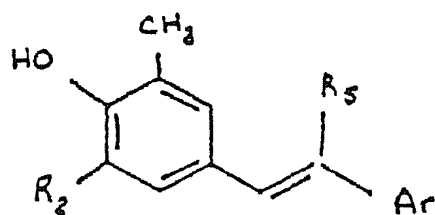
2. Suspended in 1% acacia and administered at 6 mL/kg.

3. Dissolved in dilute alkali and administered at 6 mL/kg.

4. Dissolved in distilled water and administered at 6 mL/kg.

5. Administered at 24 mg/kg instead of 30 mg/kg.

Additionally, the following compounds given by way of Example, also within the scope of the present invention, may be made with techniques known of those skilled in the art.

R₂R₅

Ar

CH₃CO₂Et

Ph

CH₃

H

2-naphthyl

CH₃

H

3-thianapthenyl

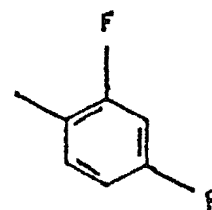
CH₃

H

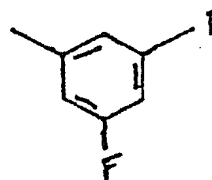
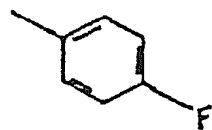
1-naphthyl

CH₃

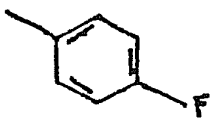
H

CH₃

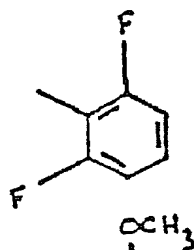
H

CH₃CH₃CH₃

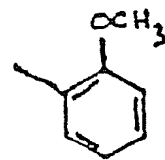
n-Bu



5 CH₃ H

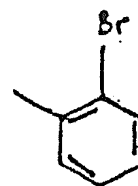


10 CH₃ H

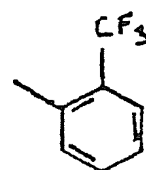


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20 CH₃ H

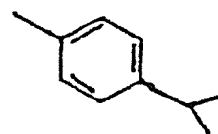


25 CH₃ H



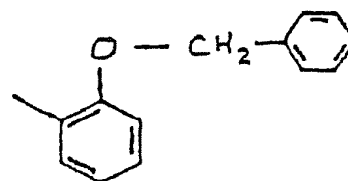
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35 CH₃ H



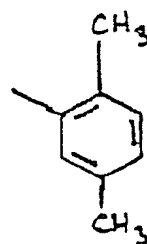
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CH₃ H



45

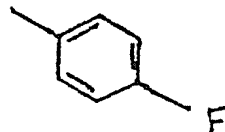
50 CH₃ H



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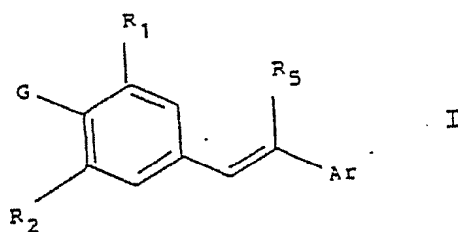
t-Bu

H



Claims

1. Compounds having the general formula I



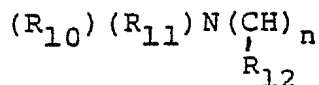
wherein

R_1 and R_2 are each independently branched or straight chained alkyl, allyl, alkoxy e.g. methoxy or halogen,

R_5 is hydrogen, alkyl or $-CO_2R_8$, wherein R_8 is hydrogen or C_1-C_3 alkyl

G is a) $-OH$

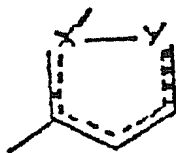
b) the group R_3CO_2- wherein R_3 is (i) HO_2C-X wherein X is an optionally substituted hydrocarbon chain with or without heteroatoms, or (ii) the group



wherein R_{10} and R_{11} are hydrogen or alkyl, R_{12} is hydrogen, alkyl or aryl possibly containing heteroatoms or R_{10} and R_{12} together form a ring, or

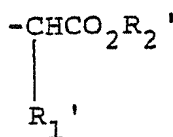
c) the group HCO_2- provided R_5 is $-CO_2R_8$ and R_8 is hydrogen or C_1-C_3 alkyl, and

Ar is an optionally substituted heteroaromatic or aromatic ring, with proviso that Ar is not



wherein --- is single or double bond and X' and Y are (i) N

(ii) NR_4 , where R_4 is H, lower alkyl,

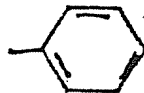


where R_1' and R_2' may be the same or different and are H or lower alkyl,
 $C(O)R_4'$ wherein R_4' is hydrogen and lower alkyl, cycloalkyl of from three to twenty carbons having from
 three to eight ring carbons, aryl or aralkyl;

(iii) O; or

(iv) S;

and the further proviso Ar is not



when R_1 and R_2 are both methyl, or another pharmaceutically acceptable ester or pro-drug thereof or salt
 or acid addition salt of the foregoing compounds.

2. A compound as recited in Claim 1 wherein Ar is 2- or 3-thienyl.

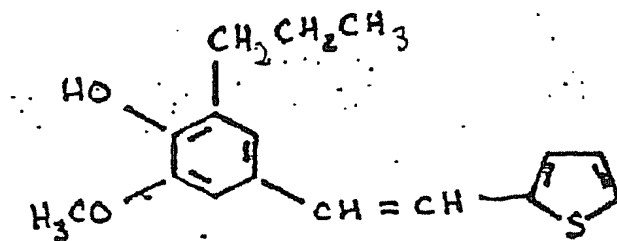
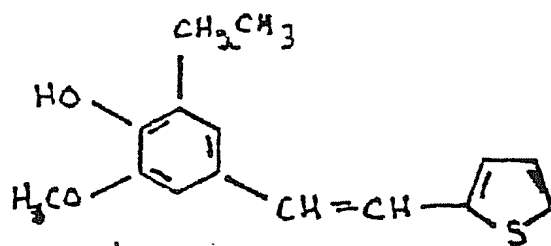
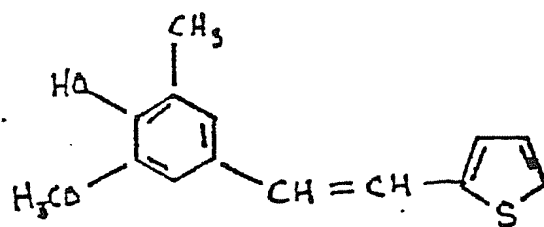
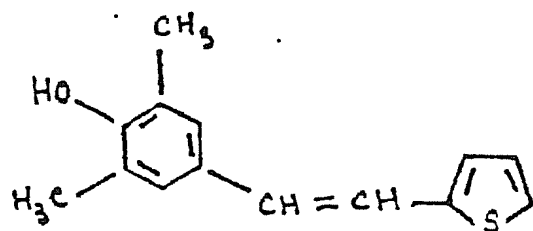
3. A compound as recited in Claim 1 wherein Ar is 2-thienyl.

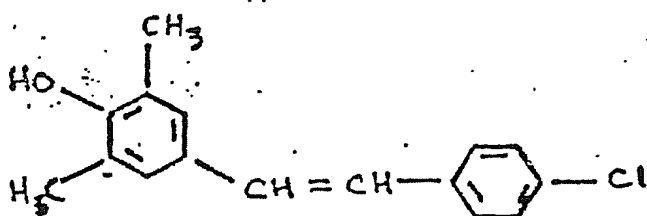
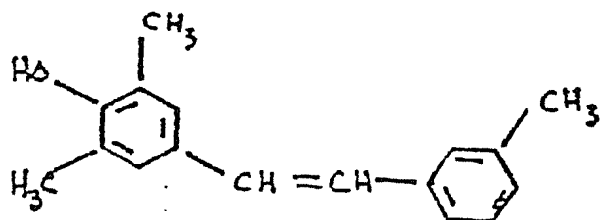
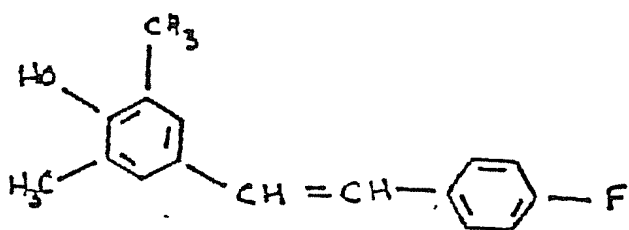
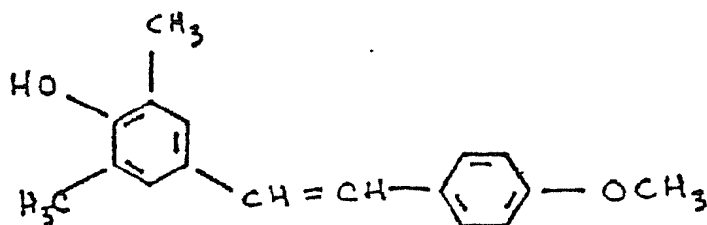
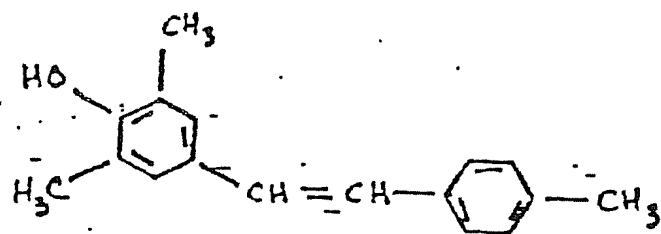
4. A compound as recited in Claim 1 wherein Ar is 1-naphthyl or 2-naphthyl.

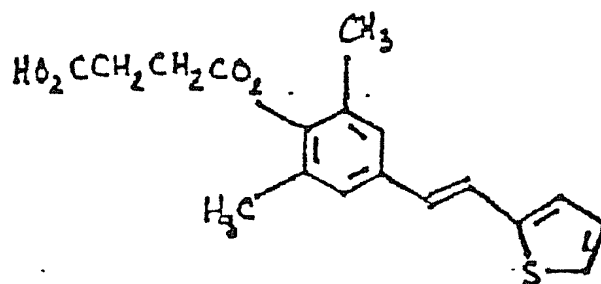
5. A compound as recited in Claim 1 wherein Ar is 3-thianaphenyl.

6. A compound as recited in Claim 1 wherein Ar is phenyl optionally mono- or poly-substituted by
 halogen, alkyl, alkoxy or trifluoromethyl.

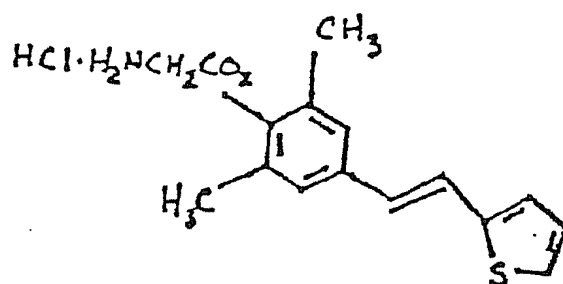
7. A compound according to in Claim 1, this compound being



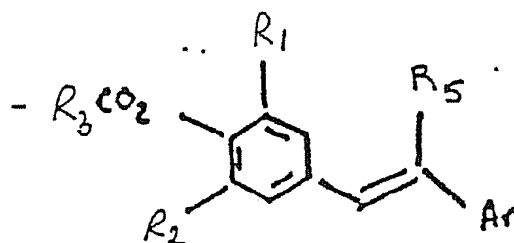




or



30 8. Compounds as recited in Claim 1 having the following formula:

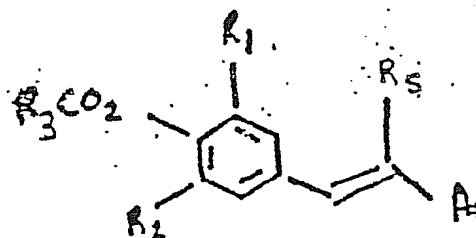


wherein R_3 is $\text{HO}_2\text{C-X}$, where X is an optionally substituted hydrocarbon chain with or without heteroatoms and

R_5 is hydrogen or $\text{C}_1\text{-C}_5$ alkyl, or CO_2R_8 , wherein

45 R_8 is hydrogen or $\text{C}_1\text{-C}_3$ alkyl, or other ester thereof, or any salt thereof.

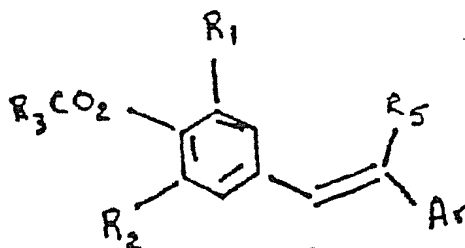
9. Compounds as defined in claim 1, having the formula



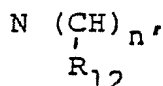
wherein R_3 is $(R_{10}) (R_{11}) N \underset{\substack{| \\ R_{12}}}{(CH)}_n$,

where R_{10} and R_{11} are each independently hydrogen or alkyl, R_{12} is hydrogen, alkyl or aryl, with or without heteroatoms or R_{11} and R_{12} form a ring, and n is an integer from one to five, and R_5 is hydrogen, or a salt thereof.

10. Compounds as recited in Claim 1 having the following formula:



wherein R_3 is HO_2C-X , where X is an optionally substituted hydrocarbon chain with or without heteroatoms, or R_3 is hydrogen, or R_3 is (R_{10}) , (R_{11}) ,



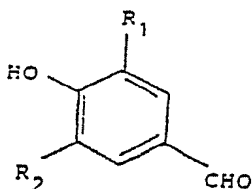
where R_{10} and R_{11} are each independently hydrogen or alkyl, R_{12} is hydrogen, alkyl or aryl, with or without heteroatoms or R_{11} and R_{12} form a ring, and n is an integer from one to five, and R_5 is CO_2R_8 , where R_8 is hydrogen or alkyl or other ester thereof, or a salt thereof.

11. A compound as defined in any one of the foregoing claims for use in the treating a disease in a warm blooded animal by inhibiting the enzyme 5-lipoxygenase.

12. A pharmaceutical composition which comprises a compound as defined in any one of claims 1 to 11 and a pharmaceutically acceptable carrier or excipient.

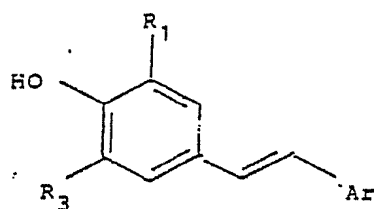
13. A method of producing a compound as defined in any one of claims 1 to 11 which comprises

a) to prepare a compound of formula 1 wherein R_5 is hydrogen and G is $-OH$, reacting a compound of formula 7



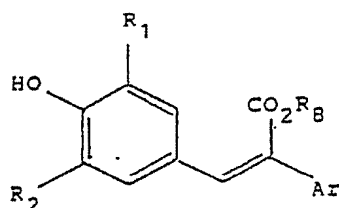
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with an aryl or heteroaryl acetic acid $8 \text{ ArCH}_2\text{CO}_2\text{H}$ 8
to yield a compound of formula 1'' having the structure



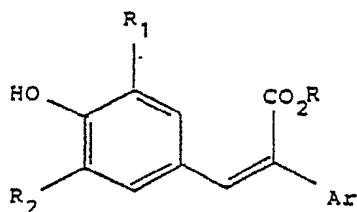
wherein Ar, R₁ and R₂ are as defined above,

15 b) to prepare a compound of formula 1, wherein R₅ is CO₂R₈ and G is -OH, reacting a compound of formula 7 as defined above with an aryl or heteroaryl acetic acid ester having the formula 9
ArCH₂CO₂R₈ 9
to yield a compound having formula 10

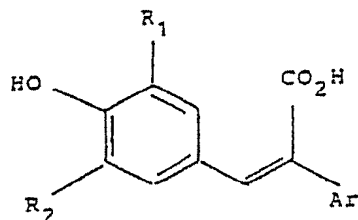


wherein Ar, R₁, R₂ are as defined above and R₈ is C₁-C₃ alkyl,

30 c) to provide a compound of formula 1 wherein R₈ is hydrogen, hydrolysing an ester of formula 10'



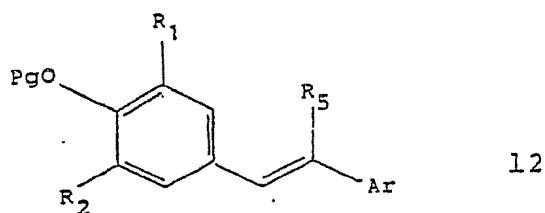
wherein R, which may be R₈ when this is C₁-C₃ alkyl, is an ester forming group capable of being removed in a manner known per se, to yield the free acid 11



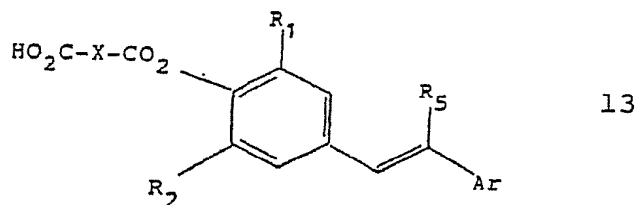
wherein Ar, R₁ and R₂ are as defined above:

55 d) to provide a compound of formula 1 wherein R₅ is hydrogen, decarboxylation of an acid of formula 11 to yield a compound of formula 1''

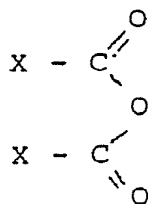
e) to yield a compound of formula 1 wherein R₅ is C₁-C₅ alkyl, deprotecting a compound having the formula 12



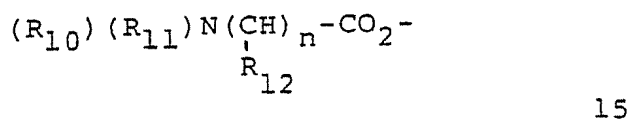
10 wherein R_1 , R_2 and Ar are as defined above and Pg is a hydroxy protecting group
f) to yield a compound of formula 13



reacting a compound of the formula 1 wherein G is OH with a compound of the formula

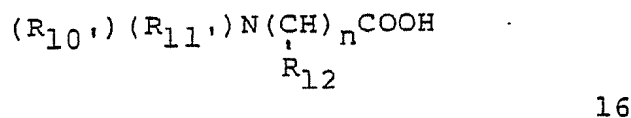


g) to prepare a compound of formula 1 wherein G is the group



as defined above,

reacting a compound of the formula 1 wherein G is OH and R_5 is alkyl or a compound of formula 10' as defined above with a compound of the formula



wherein R_1 , R_2 and R_5 are as defined above, R_{10} , and R_{11} , are hydrogen or alkyl with the proviso that if one is hydrogen the other is alkyl or a removable protecting group, and R_{12} is hydrogen, alkyl or aryl which may contain at least one heteroatom, and wherein R_{11} , and R_{12} may together form a ring, and n is an integer from one to five, and thereafter removing the groups R_{10} , and/or R_{11} , when these are protecting groups and if necessary or desired removing the group R; and thereafter, if desired, treating the product of process a) to g) by one or more of the following finishing steps in any desired order:

55

i) removing an ester group R_8 to yield a free acid

ii) esterifying a free acid to yield a pharmaceutically acceptable ester wherein the ester group is capable of being cleaved in vivo to yield the free acid

iii) forming a pharmaceutically acceptable salt of the free acid e.g. the salt of an alkali metal or alkaline earth metal e.g. sodium, potassium or calcium

iv) forming an acid addition salt of a compound of formula 1 in particular such a compound wherein

R_3 is the group $(R_{10})(R_{11})N(CH)_{n-1}R_{12}$



DOCUMENTS CONSIDERED TO BE RELEVANT			EP 89104251.7
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	US - A - 3 390 147 (R.C.JAEGER) * Totality * --	1,13	C 07 D 333/16 C 07 D 213/30 C 07 C 39/21
A	US - A - 3 188 315 (F.J.VILLANI) * Claims * --	1,13	C 07 C 43/23 A 61 K 31/33 A 61 K 31/05
D,X, P	US - A - 4 743 606 (E.S.LAZER) * Totality * --	1,11- 13	
D,X	CHEMICAL ABSTRACTS, vol. 76, no. 25, June 19, 1972, Columbus, Ohio, USA G.N.BOGDANOV et al. "Synthesis and properties of sterically hindered hydroxystyrylpyridines." page 445, column 1, abstract-no. 153 516s & Khim.Geterotsikl.Soedin. 1971, 7(12), 1660-4 --	1	
A	CHEMICAL ABSTRACTS, vol. 75, no. 3, July 19, 1971, Columbus, Ohio, USA M.FETIZON et al. "Oxidations with silver carbonate/celite. V. Oxidations of phenols and related compounds." page 416, column 1, abstract-no. 19 855c --	13	
D,A	& J.Org.Chem. 1971, 36(10), 1339-41 --		
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 16-06-1989	Examiner HOFBAUER
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			



DOCUMENTS CONSIDERED TO BE RELEVANT			EP 89104251.7
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	CHEMICAL ABSTRACTS, vol. 71, no. 5, August 4, 1969, Columbus, Ohio, USA H.D.BECKER "New stable phenoxy radicals. Oxidation of hydroxystilbenes." page 291, column 2, abstract-no. 21 813y	1	
D,A	& J.Org.Chem. 1969, 34(5), 1211-15 --		
X	CHEMICAL ABSTRACTS, vol. 72, no. 13, March 30, 1970, Columbus, Ohio, USA R.H.SIEBER "Reactions of chloro-acetaldehyde with aromatic hydrocarbons, phenols, and phenol ether." page 349, column 1, abstract-no. 66 510j	1,13	
D,X	& Justus Liebigs Ann. Chem. 1969, 730, 31-46 --		
D,X	CHEMICAL ABSTRACTS, vol. 92, no. 9, March 3, 1980, Columbus, Ohio, USA J.GIERER et al. "Studies on the condensation of lignins in alkaline media. Part III. The formation of stilbenes, arylcoumarans and diarylmethanes on treatment of spruce wood meal with alkali and white liquor in the presence of xylenols!" page 105, column 2, abstract-no. 78 366t & Acta Chem.Scand., Ser.B. 1979, B 33(8), 580-2 --	1	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 16-06-1989	Examiner HOFBAUER
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

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DOCUMENTS CONSIDERED TO BE RELEVANT			EP 89104251.7
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
P,X	EP - A2 - O 276 051 (ARIZONA STATE UNIVERSITY) * Claims * -----	1, 11, 12	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 16-06-1989	Examiner HOFBAUER
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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